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STABLE, NON-PYROGENETIC, INTRAVENOUSLY ADMINISTRABLE AQUEOUS FAT EMULSIONS CONTAINING AMINO ACIDS

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No Drawing. Continuation-in-part of application Ser. No. 284,998, Aug. 22, 1972, which is a continuation of application Ser. No. 847,396, Aug. 4, 1969, both now abandoned. This application Dec. 1, 1972, Ser. No. 311,102

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ABSTRACT OF THE DISCLOSURE

Stable infusion compositions for intravenous administration in which essential amino acids are present in the form of free bases in a fat emulsion, such as of soya bean oil. The emulsified compositions also contain soya phosphatide or egg yolk phosphatide as stabilizers. Methods for making such compositions.

This application is a continuation-in-part of copending application Ser. No. 284,998, filed Aug. 22, 1972, which latter application is, in turn, a continuation of application Ser. No. 847,396, filed Aug. 4, 1969, both are now abandoned.

The present application relates to stable infusion compositions for intravenous administration comprising essential amino acids in a fat emulsion.

In medical practice, parenteral intravenous feeding is effected in all cases in which the patient is prevented from food intake per os because of a grave disease or after an operation. The decision whether parenteral feeding has to be administered depends on the patient's general condition. In case the general condition is bad and an oral food intake cannot be expected to be possible for a longer period, it is necessary to supply all essential nutritive substances intravenously. Water, vitamins, electrolytes, trace elements, carbohydrates, amino acids, and fats are essential for a complete parenteral feeding and, in some cases, alcohol may be required as source for calories. For some years, infusion solutions containing the said substances in a form compatible with the human organism have been on the market.

As basis for a complete parenteral feeding three types of infusion solutions are known, viz carbohydrate solutions, amino acid solutions, and fat emulsions. To these solutions there are added vitamins, electrolytes and trace elements which constitute, as far as their amount is concerned, only a small part of the nutrition as compared to the three main food carriers.

The total demand of calories and nitrogen must be satisfied by parenteral feeding. The single nutrients have a quite different nutritive value. Thus, for example, 1 g. of carbohydrate corresponds to about 4 kcal., 1 g. of alcohol corresponds to about 7 kcal. and 1 g. of fat corresponds to about 9 kcal. Amino acids, which supply 4 kcal. per 1 gram, should, however, be present as elements for the synthesis of proteins. This, however, is only possible if the amount of calories supplied by fats and carbohydrates covers the energy requirements of the organism. In case the amount of calories is insufficient, amino acids are also utilized as source for calories, this effect being, however, undesirable and leading to a negative nitrogen balance.

Thus, in clinical practice, complete parenteral feeding is effected by administering three separated infusion solutions. Because of the better compatibility with the wall of the vein, hyper-osmolar amino acid solutions are frequently administered simultaneously with a fat emulsion through the same needle or the same catheter. This kind of administration, however, necessitates the use of special tube systems and, simultaneously, the control of two bottles of infusion solutions by the hospital staff.

It would, therefore, be an important simplification if it would be possible to combine fats and amino acids in one single emulsion. Another advantage of such a combined infusion solution would be that the supply of water to the organism would be reduced. Manufacturers of infusion solutions usually recommend administering the amino acid solutions and the fat emulsions in a volume ratio of 2 to 1, i.e., for example, 1000 ml. of a 5% commercial amino acid solution and 500 ml. of a commercial 10% fat emulsion are administered. If a combined emulsion, containing, per 1000 ml., 50 g. of amino acids and 50 g. of fat could be successfully prepared, the amount of liquid supplied would be reduced by 33%. This reduction would mean an important relief for the patient since the danger of overhydration would be reduced. Moreover, the margin for the intravenous administration of, for example, carbohydrates or of solutions which regulate the electrolyte metabolism, would be increased.

However, fat emulsions or, generally, oil-in-water emulsions, physically and chemically, constitute a metastable system which is converted by external disturbances, for example, by the effects of temperature or the addition of electrolytes or colloids, into an energetically stable state. This process is manifested in the separation of the phases, designated as "creaming." Since amino acids also may be regarded as electrolytes because of their dipolar-ionic character, it could be expected that the stability of fat emulsions containing amino acids would be considerably reduced.

Now it has been found that when certain conditions are observed, stable, non-pyrogenic, aqueous fat emulsions containing amino acids, which emulsions are administered intravenously, can be obtained by dissolving in water the essential (and, if desired or required, additionally, non-essential) amino acids which are necessary for the parenteral feeding of humans, in their D, L- or L-forms and in amounts and concentrations favorable to the human organism, and by emulsifying the fat suitable for infusions, in the required amount, in the said amino acid solution by means of an emulsifier admissible, compatible and suitable for these purposes. Furthermore, the aqueous phase may also contain glycerin and/or other polyalcohols, such as sorbite or xylite.

The stable aqueous fat emulsions containing amino acids may also be obtained by preparing the aqueous amino acid solution and the fat emulsion separately and by subsequently mixing the two components.

In contrast to microorganisms and other lower organisms, the animal and especially the human organism is not able itself to synthesize all amino acids necessary for the synthesis of proteins. Eight so-called essential amino acids are known which must be present in food if serious disturbances in protein metabolism are to be avoided. It is important that amino acid solutions contain, for parenteral feeding, all essential amino acids such as lysine, methionine, phenylalanine, leucine, isoleucine, valine, tryptophane, and threonine in sufficient quantities. They may advantageously additionally contain other, so-called nonessential, amino acids, for example glycine, alanine, proline, histidine, or diamino valeric acid and serine. The quantitative relation of the single amino acids should be selected in a manner that a well-balanced or slightly positive nitrogen balance is possible in the or-